

United Research Laboratories, Inc. Mutual Pharmaceutical Company, Inc.

1100 Orthodox Street Philadelphia, PA 19124

215-288-6500 www.urlmutual.com

1000 TO THE - 2:00

February 4, 2004

Dockets Management Branch Food and Drug Administration (HFA-305) Department of Health and Human Services 5630 Fishers Lane, Room 1061 Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, on behalf of Mutual Pharmaceutical Company in accordance with Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.93 to request that the Commissioner of Food and Drugs permit the filing of an Abbreviated New Drug Application (ANDA) for a drug that has the same active ingredient, route of administration, and dosage strengths as a drug listed in FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluation" (i.e., the Orange Book), but differs in dosage form.

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration make a determination that the drug product, Doxycycline Hyclate Capsules, 75mg and 100 mg, is suitable for evaluation under an ANDA. The referenced product is Doryx® Capsules, 75 mg and 100 mg (NDA 50-582). This Petition requests a change in dosage from that listed in the Orange Book as "capsule, coated pellets, oral" to an oral capsule containing powder or other fill that is different than coated pellets.

B. <u>Statement of Grounds</u>

The Federal Food, Drug and Cosmetic Act provides for the submission of an ANDA for a drug product that differs in dosage form from that of the listed drug provided the FDA has approved a petition that proposed filing such an application. A copy of the most recent on-line listing of the electronic "Approved Drug Products with Therapeutic Equivalence Evaluations", included as Attachment 1, lists the reference drug, Doryx® Capsules, by Mayne Pharma USA. That listing further specifies that the dosage form of the reference drug is "capsule, coated pellets, oral".

The proposed drug product is an oral capsule dosage form, as is the reference listed drug (RLD), and is in the same dosage strengths as the RLD. The difference between the proposed drug product and the RLD, which is the subject of this petition, is that the proposed drug product will contain a powder or other material that is not comprised of coated pellets. The proposed product contains the same active ingredient as the RLD and is intended for the same route of administration. Thus, the proposed product will be labeled with the same dosage recommendations as the RLD and is expected to have the same therapeutic effect when used as indicated in the approved labeling.

In addition, the labeling for the proposed product is expected to be substantially the same as the RLD with the exception of changes necessitated by the fact that the product is manufactured by a different company, the product does not contain coated pellets, the product is referred to by the generic name Doxycycline Hyclate Capsules rather than the Doryx® brand name, and the product's appearance and "How Supplied" information are different. The initial draft labeling and the approved labeling for the RLD are included as Attachments 2 and 3, respectively.

20041.0054

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C. **Environmental Impact**

The petitioner claims a categorical exclusion under 21 CFR 25.31.

Economic Impact D.

Pursuant to 21 CFR 10.30(b), the economic impact information will be submitted if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,

Robert Dettery

Vice President, Regulatory Affairs **Mutual Pharmaceutical Company**

1100 Orthodox Street Philadelphia, PA 19124 (215) 288-6500

- Attachments: 1) electronic Orange Book listing
 - 2) draft labeling
 - 3) Doryx® Capsules labeling

G. Davis (Office of Generic Drugs) Cc:

ATTACHMENT 1

Search results from the "Rx" table for query on "050582."

Active Ingredient:

DOXYCYCLINE HYCLATE

Dosage Form; Route:

Capsule, Coated Pellets; Oral

Proprietary Name

DORYX

Applicant:

MAYNE PHARMA USA

Strength:

EQ 100MG BASE

Application Number:

050582

Product Number:

001

Approval Date:

JUL 22, 1985

Reference Listed Drug: RX/OTC/DISCN:

Yes RX

TE Code:

AB

Patent and Exclusivity Info for this product: Click Here

Active Ingredient:

DOXYCYCLINE HYCLATE

Dosage Form; Route:

Capsule, Coated Pellets; Oral

Proprietary Name

DORYX

Applicant:

MAYNE PHARMA USA

Strength:

EQ 75MG BASE

Application Number:

050582

Product Number:

002

Approval Date:

AUG 13, 2001

Reference Listed Drug:

No

RX/OTC/DISCN:

RX

TE Code:

Patent and Exclusivity Info for this product: Click Here

Thank you for searching the Electronic Orange Book

Return to Electronic Orange Book Home Page

Rx Only

DOXYCYCLINE HYCLATE CAPSULES USP

DESCRIPTION

Doxycycline Hyclate Capsules contain doxycycline hyclate for oral administration. Inactive ingredients are croscarmellose sodium, D&C Red #28, FD&C Blue #1, gelstin, magnesium stears cellulose, titanium dioxide, and anhydrous lactose Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline and available as doxycycline derives from oxyletracycline and available as doxylytims hydrist. The chemical designation of this light-yellow crystalline powder is alpha-6-desoxy-5-oxytetra-cycline. Doxycycline has a high degree of lipoid soluability and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

CLINICAL PHARMACOLOGY

CLINICALPHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plusma proteins in varying degree. They are concentrated by the liver in the bile and excreted in the urine and faces at high concentrations and in a biologically active form. Doxycycline is wirtually completely absorbed after oral administration. Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/mL of doxycycline at 2 hours decreasing to 1.45 mcg/mL at 24 hours. Exerction of doxycycline by the kidney is about 40%772 hours in individuals with normal function (creating contents a server in a content of contents of the property of the contents of the cont nine clearance about 75 mL/min). This percentage excretion may fell as low as 1-5%/72 hours in individuals with severe i insufficiency (creatinine clearance below 10 mL/min)

renal insufficiency (creatinine clearance below 10 mL/min). Studies have shown no significant difference in serum half-life of doxycytine (range 18-22 hours) in individuals with normal and severely impaired renal function. Hemodialysis does not alter serum half-life. Microbiology: Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative organisms. The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is common. Susceptibility Tests: Diffusion Techniques: The use of antibiotic disc susceptibility test, methods which measure zone

diameter gives an accurate estimation of susceptibility of sms to doxyoyoline hyciste. One such standar procedure has been recommended for use with discs for testing antimicrobials. Doxyoyeline 30mog discs should be used for the determination of the suseptibility of organisms to doxycycline.

suscribility of organisms to dexycycline.

With this type of procedure, a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptible ity" suggests that the organism would be susceptible if high-dorage is used or if the infection is confined to tissue and fluids (e.g., urine) in which high antibiotic levels are obtained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With the doxycycline disc, a sone of 16 mm or greater indicates susceptibility, sone-sizes of 12 mm or less indicate resistance, and sone sizes of 13 to 15 mm indicate intermediate susceptibility.

tibility.
Standardized procedures require the use of laborative discountries of the contraction of the contr premarance precurers require the tiss of moderatory con-trol organisms. The 80 mg tetracycline disc should give zone diameters between 18 and 25 mm for E. coll ATCC 25922. The 30 mg doxycycline disc should give zone diameters be-tween 23 and 28 mm for E. coll ATCC 25922, and be-tween 18 and 24 mm for E. coll ATCC 25922.

tween 18 and 24 mm for a con ATUL zoneza.

Dilution Techniques: A bactarial isolate may be considered susceptible if the MIC (minimal inhibitory concentration) value for decreycyline is less than 4 meg/mL. Organisms are considered resistant if the MIC is grister than 12.5 meg/mL. MICs greater than 4.0 meg/mL and less than 12.5 meg/mL indicate interfiedints susceptibility.

12.5 mag/mL indicate intermediate.susceptibility.

As with standard diffusion methods, dilution procedures require the use of laboratory control mechanisms. Standard doxycellae powder should give MIC values in the range of 0.25 mag/mL and 1.0 mag/mL for Sciences ATCC. 25922.

Ror E. coli ATCC 25922 the MIC range should be between 1.0 mcg/mL and 4.0 mcg/ml

INDICATIONS AND USAGE

Doxycycline is indicated in infections caused by the follo

ing microorganisms;
Rickettsiae (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick

Eycoplama pneunioniae (PPLO). Eaton's agent). Agents of psittacosis and arnithosis. Agents of lymphogranuloma venereum and granulo

The spirochetal agent of relapsing fever (Borrelia recur

rentia.
The following gram-negative microorganisms:
Haemophilus duereyi (chancroid)
Yersinia postis (formerly Pasteurella pestis)
Francisella tularensis (formerly Pasteurella tularensis) Bartonella bacilliformia

Bartonella bacilliformis
Bactaroides species
Vibrio chelerae (farmerly Vibrio comma)
Campylobacter fetus (farmerly Vibrio fetus)
Brucella species (in conjunction with streptomycin)
Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.
Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when becteriological testing indicates appropriate susceptibility to the drug. the drug

Escherichia coll . Enterobacter aerogenes (formerly Aerobacter aerogenes)

Skigella species Mima species and Herellea spec Міта вре

Mamaphilus influence (respiratory infections)

Klebsialla species (respiratory and urinary infections)

Duycycline is indicated for treatment of infections caused
by the following gram-positive microgramians when bactariological testing indicates appropriate susceptibility to the

drug! Streptococcus apecies

Streptococcus species:
Up to 44 percent of strains of Streptococcus pyogenes and 74 percent of Streptococcus faccalis have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the ofignism has been demonstrated to be susceptible.
For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, in-

lytic streptococci, penicillin is the usual d cluding prophylaxis of rheumatic fever. Diplococcus pneumonias.

Diplacectus pneumonias. Sipplylococus unrus fractions). Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

Anthrax due to Bacillus anthracis, including inhalational

anthren (post-exposure): to reduce the incidence or prog sion of disease following exposure to acrosolized Baci

antaraces.

When paticillin is contraindicated, decrycycline is an alternative drug in the treatment of infactions due to:

Treponema pallidum and Treponema perfenue (syphilis and yaws)

ria monocytogenes

Clostridium species
Fuschaeterium fusiforme (Vincent's infection)

In acute intestinal amebiasis, dozveveline may be a useful

In severe acne, doxycycline may be useful adjunctive ther-

app.
Doxyeyeline is indicated in the treatment of trachems, al-though the infectious agent is not always eliminated, as

induced by immunofluorescence.

Inclusion conjunctivitis may be treated with oral doxyoviline alone, or with a combination of topical agents. Doxyoviline is indicated for the treatment of uncomplicated trethral, endocarvical or rectal infections in adults caused by Chlamydia trachometic.

oxycycline is inidicated for the treat proxycycine is uniceased for the treatment or immensioned urethritis caused by Chlamydis trachomatic and Unexplained uredysterm and for the treatment of seate episidy mo-exchitis caused by Chlamydia trachomatics.

genococcal infections in adults (except for smorecial infec-tions in men), the genococcal arthritis-dermatitis syndroms and acute spididymo-orchitis caused by N. genorrhoese.

CONTRAINDICATIONS

The drug is contraindicated in persons who have shown by personalityly to any of the tetracyclines. WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INEANCY AND CHILDROOD TO THE AGE OF 5 YEARS) MAY CAUGE FERMANENT DISCOL-ORATION OF THE TEETH (YELLOW-GRAY-BROWN). ORATION OF THE TREETH (YELLOW-HRAY-HROWN, This adverse reaction is more common during long term use of the drugs but has been observed following repeated short term courses. Enamel hypoplasis has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD.NOT HE USED IN THIS AGE GROUP, EXCEPT FOR ANY THRAX, INCLUDING INHALATIONAL ANTHRAX. (POST EXPOSURE), UNILESS OTHER DEUGS ARE NOT LIRELY TO BE EFFECTIVE OR ARE CONTRAINDI-CATED

CATED.

Results of milinal studies indicate that fetracyclines cross the placents, are found in fatal tissues and can have turb effects on the developing fatus (often related to retardation of akoletal development). Evidence of ambryotoxicity has been noted in animals treated early in pregnancy, if any telegraphic is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of potential hazard to the fatus.

As with other betracyclines, dozyoycline forms a stable eal-clum complex in any bone-forming tissue. A decrease in the

apprised of potential nazard to the setue. As with other 'btracycline, ducyocycline forms a stable cal-cium complex in any bone-forming tissue. A decrease in the fibule growth rate has been observed in promatures givid, oral tetracycline in doese of 25 mg/kg every sk norm. This rüsction was shown to be reversible when the drug was dis-

communes.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetrareptines. Patients age to be exposed to direct smallest or ultravialet light abould be advised that this resistion can obser with tetracycline drugs, and treatment should be discontinued at the first evidence of skin crythams.

The antianabolic action of the tetracyclines m increase in BUN. Studies to date indicate that this does not r with the use of doxycycline in patients with impaired

PRECATITIONS. .

PRECAUTIONS

As with other antiblotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antiblotic should be discontinued and appropriate therapy instituted.

All infections due to group A beta-hemolytic streptocood should be treated for at least 10 days.

Laboratory tester. In venereal disease when coarists syphilis is suspected, dark-field examination should be done before treatment is started and the blood serology repeated

before treatment is started and the blood serology repeated monthly for at least 4 months. In long term therapy, periodic leboratory evaluation of organ systems, including hematopoietic, renal and hepatic Studies should be performed.

Drug interactions: Because tetracyclines have been shown to depress plasma prothrombin activity, positents who are on anticongulant therapy may require downward adjustment of their anticongulant decaye.

Since bacteriostatic drugs may interfere with the becomedial action of penticilla, it is advisable to seroid giving totacyclines in conjunction with penticilia,

For concentiont therapy with antacids or iron-containing preparations and food see DOSAUE AND ADMINISTRATION section.

Carolinogenesis, inutagenesis, impairment of tartility:

THOM section.

Carolnogenesis, inutagenesis, impairment of fartility.

Long-term studies are currently being conducted to determine whether tetracyclines have carcinogenic potential. Animal studies conducted in rats and mice have not provided conclusive evidence that tetracyclines may be carcinoge or that they impair fertility. In two mammalian cell assa (L51784 mouse lymphoma and Chinese hamster lung or in siro), positive responses for mutagenicity occurred at concontrations of 50 and 10 mcgmL, respectively. In hu-mans, no association between tetracyclines and these effects

Pregnancy: Pregnancy Category D (see WARNINGS see

tion). Nursing mothers: Tetracyclines are present in the milk of lactating women who are taking a drug in this class, Be-cause of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the median (see WARNINGS section).

edianic use: See WARNINGS and DOSAGE AND AD-MINISTRATION sections.

ADVERSE REACTIONS

ADVERSE REACTIONS

The to are doxyevelines virtually complete absorption, side effects to the lower howel, particularly diarrhea, have been infrequent. The following adverse-reactions have been obserted in patients receiving tetracyclines:

fastrointestinal: Anerexia, nausea, vomiting, diarrhea, gizidita, dysphagia, enterocolitis, and inflammatory leatons (with monitial overgrowth) in the anogenital region. These reactions have been caused by both the oral and paranteral diministration of tetracyclines. Eare instances of ecophagistal and esophageal ulcerations have figen reported in patients, receiving capsule and tablet forms of drugs; in the tetracycline class. Most of these patients took medications immediately before going to bed (see DOSAGE AND ADMINISTRATION section).

Him Manulopanular and crythematous rashes. Exfoliative

ministriction section).

Him Maculopapular and crythematous rashes. Exfoliative demaitits has been reported but is uncommon. Photosensitivity is discussed above (see WARNINGS section).

Regal Involve Rise to HTML Land.

Renal backty: Rise in HUN has been reported and is appar-ially dose-related (see WARNINGS section).

inthy dose-related (see WARNINGS section).

Hypersensitivity reactions: Unticaria, angioneurotic edema, insigniarii, anaphylactoid purpura, pericarditis, and exacellesition of systemic lupus enythematesus.

Bulgitig fostenals in infants and benign intracratical hyperinsign in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the
first was discontinued.

Bilod: Hamolytic anemia, thrombocytopenia, neutropenia,
ind solmophilia have been reported with tetracyclines.

When itsens over undowed periods, extracyclines have been

ma componium nave been reported with tetracyclines, have been phoried to produce incomplace microscopic discoloration whereas to produce incomplace microscopic discoloration of thyroid glands. No altiormalities of thyroid function are moved to occur.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINIS-THE OSUAL JUNEIS AND FREQUENCY OF ADMINISTRATION OF DOXYOYCLINE DIFFERS FROM THAT OF THE OTHER TETTÄ, CYCLINES. EXCEPDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults The usual dose of any december 1997.

commenced Dosage MAY RESULT IN AN INdirection in collection of Side Refection.

Achieve the usual dose of oral decryocities is 200 mg on the
first day of treatment (administered 100 mg every 12 hours)
followed by a maintenance dose of 100 mg/day. The mainteplacement of the property of the management of more severe
injections (particularly chronic infections of the urinary
match, 100 mg every 12 hours in the management of more severe
injections (particularly chronic infections of the urinary
match, 100 mg every 12 hours is recommended.

For pediatric patients above eight yearn of age: The recommended desage schedule for pediatric patients weighing 100
pounds or less is 2 mg/h of body weight divided into two
doses on the first day of treatment, followed by 1 mg/h of
body weight given as a single daily dose or divided into two
doses on subsequent days. For more severe infections up to
2 mg/h of body weight may be used. For pediatric patients
fewer 100 pounds, the usual adult dose should be used.
Uncomplicated gonocyccal infections in adults (except apprectal infections in men): 100 mg, by mouth, twice-a-day for
7 days. As an alternate single visit dose, administer 300 mg
data followed in me hour by a second 300 mg dose. The dose
may be administered with food, including milk or carbonated beverage, as required.

may be administered with 100d, including milk or carnon-ated bewrape, as required.

Acute epididymo-orchitis caused by N. gonorrhocae: 100 mg. by mouth, twice-a-day for at least 10 days.

Primary and secondary syphilis: 300 mg a day in divided doses for at least 10 days.

Decomplicated urethral, endocervical, or rectal infaction in shulls caused by Chlanydla trachomatis: 100 mg by mouth, twice-a-day for at least 7 days.

Nongonococcal urethritis caused by C. truchomatis and U. arealyticum: 100 mg, by mouth, twice-a-day for at least 7 days.

asys.

Acute epididymo-orchitis caused by C. trachomatis: 100 mg,
by mouth, twice-a-day for at least 10 days.

Inhalational anthrax (post-exposure):

ADULTS: 100 mg, of doxycycline, by mouth, twice a day for

CHILDREN: weighing less than 100 lb (45 kg); 1 mg/lb (2.2 mg/kg) of body weight, by mouth, twice a day-for 50 days. Children weighing 100 lb or more should receive the lifabit does.

and nose. The therapeutic antibacterial serum activity will usually perfect for 24 hours following recommended desage. When used in streptococcal infections, therapy should be

Administration of adequate amounts of fluid along with cap-tals and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of scophageal irritation and discretion (see ADVERSE RE-ACTIONS section).

b gastric irritation occurs, it is recommended that daycycline be given with food or milk. The absorption of daycycline is not markedly influenced by simultaneous in-jestion of food or milk.

Concomitant therapy: Antacids containing aluminum, cal-cium or magnesium, sodium bicarbonate, and iron-contain-ing preparations should not be given to patients taking oral tetraccilines.

Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment

HOW SUPPLIED:

Doxycycline Hyclate Capsules are available as follows:

Equivalent to 75 mg Doxyoycline (opaque crange and greec capsule) in: Bottles of 50 capsules, NDC XX-XX imprinted Mutual XXX Bottles of 500 capsules, NDC XX-XX imprinted Mutual XXX

Equivalent to 100 mg Doxycycline (opame yellow and light blue capsule) in: Bottles of 50 capsules, NDC XX-XX imprinted Mutual XXX Bottles of 500 capsules, NDC XX-XX imprinted Mutual XXX

Store at controlled room temperature 15°-30°C (59°-86°F).

DISPENSE IN TIGHT LIGHT-RESISTANT CONTAINER

REFERENCES.

HEFFERENCES.

1. NCCLS Approved Standard:
M2-A8, Vol. 4. Performance Standards for Antimicrobial
Disk Susceptibility Tests, Third Edition: available from the
National Committee for Clinical Laboratory Standards, 771.
East Lancaster Avenue, Villanova, Ph. 19085
2. CDC Sexuality Transmitted Diseases Treatment, GuideHune 1982.

lines 1982

Manufactured by: MUTUAL PHARMACEUTICAL CO., INC. Philadelphia, PA 19124 USA.

Revised: XXX

DORYX® (coated doxycycline hyclate pellets)

DESCRIPTION

DESCRIPTION

DORYK® Capsules contain specially coated pellets of doxycycline hydlete for oral administration. Also contains lactose, NF; microcrystalline cellulose, NF; povidone, USP. The capsule shell and/or hand contains ED and C blue No. 1; FD and C yellow No. 6; D and C yellow No. 10; gelatin, NF; silicon dioxide; sodium lauryl sulfate, NF, titanium dioxide, USP. Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline and available as doxycycline byclate. The chemical designation of this light-vellow crystalline bowder is alpha-fidesony-favorateric synthetic. yellow crystalline powder is alpha-6-desoy-5-oxytetra-cycline. Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum, Doxycycline will not degrade into an epianhydro form.

CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile and excreted in the urine and feces at high concentrations and in a biologically active form.

Doxycycline is virtually completely absorbed after oral administration. Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/mL of doxycycline at 2 hours decreasing to 1.45 mcg/mL at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 mL/min). This percentage excretion may fall as low as 1–5%/72 hours in individuals with severe renal insufficienty (creatinine clearance below 10 mL/min). Studies have shown no significant difference in serum half-life of doxycycline (range 18–22 hours) in individuals with normal and severely impaired renal function. Henodialysis does not alter serum half-life.

Microbiology: Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide

of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative organisms. The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is co Susceptibility Tests: Diffusion Techniques: The use of antibiotic disc susceptibility test methods which measure zone diameter gives an accurate estimation of susceptibility of organisms to DORYKO. One such standard procedure has been recommended for use with discs for testing antimitrobials. Doxyceline 30 meg discs should be used for the determination of the susceptibility of organisms to

termination of the suspeptibility of organisms to doxycycline. With this type of procedure, a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therspy. A report of "intermediate susceptiblity" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissuic and diuds (e.g., urine) in which high antibiotic levels are obtained, A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With the doxycycline disc, a sone of 16 mm or greater indicates susceptibility, zone-sizes of 12 mm or less indicate resistance, and zone sizes of 13 to 15 mm indicate intermediate susceptibility.

nomity.

Standardised procedures require the use of laboratory control organisms. The 30 mcg tetracycline disc should give zone diameters between 19 and 28 mm for S. aureus ATCC 25923 and between 18 and 25 mm for E. coli ATCC 25922. The 30 mcg doxycycline disc should give zone diameters between 28 and 29 mm for S. aureus ATCC 25923, and between 28 and 29 mm for S. aureus ATCC 25923, and between 28 and 29 mm for S. aureus ATCC 25923.

tween 28 and 28 mm for S. cureus ATCC 25923, and between 18 and 24 mm for S. cureus ATCC 25922.
Dilution Techniques: A hacterial isolate may be considered succeptible if the MIC (minimal inhibitory concentration) value for doxycycline is less than 4 mcg/mL. Organisms are considered resistant if the MIC is greater than 12.5 mcg/ml. MICs greater than 4.0 mcg/ml. and less than 12.5 mcg/ml, indicate interificiate, succeptibility. As with standard diffusion methods, dilution procedures require the use of laboratory control mechanisms, Standard doxycycline powder should give MIC values in the range of 0.25 mcg/ml. and 1.0 mcg/ml. for S. cureus ATCC 25923. For E. coli ATCC 25922 the MIC range should be between 1.0 mcg/ml. and 4.0 mcg/ml. 1.0 mcg/mL and 4.0 mcg/mL

INDICATIONS AND USAGE

Doxycycline is indicated in infections caused by the follow-

ing microorganisms:
Rickettsiae (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fevers).

Mycoplasma pneumoniae (PPLO, Eaton's agent).

Agents of petitacosis and ornithosis. Agents of lymphogranuloms venereum and granulo inguinale:

The spirochetal agent of relapsing fever (Borrelia recur-

the spirochem agent of tempong rote (control rentis).
The following gram-negative microorganisma:
Haemophilus ducreyi (chancroid)
Yersinia postis (formerly Pasteurella pestis)
Francisella tularensis (formerly Pasteurella, tularensis)

Bartonella bacilliformis

Bartonella bactiforms
Bacteroides especies
Vibrio cholerue (formerly Vibrio comma)
Campylobacter fetus (formerly Vibrio fetus)
Brucella species (in conjunction with streptemycin) Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines. culture and susceptibility testing are recommended.

Doxyevline is indicated for treatment of infections caused by the following gram-negative microorganisms, when higher teriological testing indicates appropriate susceptibility to

the drug: Escherichia coli

Enterobacter aerogenes (formerly Aerobacter aerogenes).

Shigella species

Mima species and Herellea species

Haemophilus influenzae (respiratory infections)

Klebiella species (respiratory infections)

Klebiella species (respiratory and urinary infections)

Doxycycline is indicated for treatment of infections caused by the following gram-positive missasses. by the following gram-positive microorganisms when bacte-riological testing indicates appropriate susceptibility to the drug:

Streptococcus species: Up to 44 percent of strains of Streptococcus pyogenes and 74 percent of Streptococcus faccalis have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

For upper respiratory infections due to group A beta-hemp-lytic streptococci, penicillin is the usual drug of choice, in-cluding grophylaxis of rheumatic fever.

Diplocóccus pneumoniae.

Symphylosceus aureus (respiratory, skin and soft-tissue infections). Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection. Anthrax due to Bacillus anthracis, including inhalational anthrax (post-exposure); to reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis.

sion of disease innowing exposure to accommodate anthracie.
When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to Treponema pollidum and Treponema perteñue (syphilis

Listeria monocytogenes

Clostridium species
Fusobacterium fusiforme (Vincent's infection)

Actinomyces species In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

In severe acne, doxycycline may be useful adjunctive ther-

Dayweyeline is indicated in the treatment of truck

Doxycycline is indicated in the treatment of trachoma, al-though the infectious agent is not always eliminated, as judged by immunofluorescence, Inclusion conjunctivitis may be treated with oral, doxycycline alone, or with a combination of topical agents, Doxycycline is indicated for the treatment of uncomplicated

Doxycycline is indicated for the treatment or uncompicated urethral, endocarvical or rectal infections in adults caused by Chlamydia trachomatia.²
Doxycycline is indicated for the treatment of nongonococcul urethritis caused by Chlamydia trachomatis and Urganiama urealyticum and for the treatment of neute epidicalization.

plasma urealyticum and for the treatment of acute epididi-mo-orchitis caused by Chlamydia trachomatia.²
Daxycycline is indicated for the treatment of uncomplicated gonococcal infactions in adults (except for ancrecial infe-tions in men), the gonococcal arthritis-derinatitis syndrome and acute epididymo-orchitis caused by N. ganorrheea.²

CONTRAINDICATIONS

The drug is contraindicated in persons who have shown hy-personsitivity to any of the tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST. HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long term use of the drugs but has been observed following repeated short term courses. Examel hypoplasis has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD.NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALTIONAL ANTHRAX (POSTEXROSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED. THE USE OF DRUGS OF THE TETRACYCLINE CLASS

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of potential hazard to the fetus. As with other extracyclines, doxycycline forms a stable estimate complex in any bone-forming tissue. A decrease in the fibula growth rate hias been observed in prematures given oral tetracycline in deses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

continued.

Photosensitivity manifested by an exaggerated sunburn re-action has been observed in some individuals taking tetra-cyclines. Patients apt to be exposed to direct sunlight or un-traviolet light should be advised that this relation can occur with tetracycline drugs, and treatment should be discontitued at the first evidence of skin erythems.

The antianabolic action of the tetracyclines may cause as increase in BUN. Studies to date indicate that this does no occur with the use of doxycycline in patients with impaired

PRECAUTIONS ...

As with other antibiotic preparations, use of this drug may

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted. All infections due to group A beta-hemolytic streptococcishould be treated for at least 10 days.

Leboratory tests: In veneral disease when coexistent syphilis is suspected, dark-field examination should be done before treatment is started and the blood serology repealed earthly fixed before the started and the blood serology repealed.

before treatment is started and the blood serology repealed monthly for at least 4 months.

In long term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, reual and hepsile studies should be performed.

Drug Interactions: Because tetracyclines have been shows to depress pleasing prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticongulant dosage.

Since bacteriostatic drugs may interfere with the bacterical action of penteillin, it is advisable to sword giving tetracyclines in conjunction with penteillin.

For concomitant therapy with antacids or iron-containing preparations and food see DOSAGE AND ADMINISTRATION section.

Carcinogenesis, mutagenesis, impairment of fertility:
Long-term studies are currently being conducted to determine whether tetracyclines have carcinogenic potential. Animal studies conducted in rats and mice have not provided conclusive evidence that tetracyclines may be carringenic conclusive evidence that tetracyclines may be carchogenic or that they impair fertility. In two mammalian cell sissays (L51784 mouse lymphoma and Chinese hamster lung cells in vitro), positive responses for mutagenicity occurred at concentrations of 60 and .10 mcg/ml, respectively. In humans, no association between tetracyclines and these effects have have severed.

Pregnancy: Pregnancy Category D (see WARNINGS see

Nursing mothers: Tetracyclines are present in the milk of lactating women who are taking a drug in this class. B cause of the potential for serious adverse reactions in nur ing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue that drug, taking into account the importance of the drug to the mother (see WARNINGS section).

mother (see WARNINGS section).

Pediatric use: See WARNINGS and DOSAGE AND ADMINISTRATION sections.

ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side mere oral converteemes virtually complete absorption, note effects to the lower bowel, particularly diarrhee, have been infrequent. The following adverse reactions have been ob-served in patients receiving tetracyclines:

served in patients receiving tetracyclines:

Rastrointestinal: Anorexia, nauses, vomiting, diarrhea,
gidestis, dysphagia, enterocolitis, and inflammatory lesions
(with monilial overgrowth) in the anogenital region. These
reactions have been caused by both the oral and parenteral
dianinistration of tetracyclines. Rare instances of esophagiis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the ter-ricycline class. Most of these patients took medications immediately before going to bed (see DOSAGE AND AD-MINISTRATION section).

Skin: Maculopapular and erythematous rash dermatitis has been reported but is uncommon. Photosensitivity is discussed above (see WARNINGS section).

Renal toxicity: Rise in BUN has been reported and is apparantly dose-related (see WARNINGS section).

mity dose-related (see WARNINGS section). Hypersensitivity reactions: Urticaria, angioneurotic edema, shappylaxia, anaphylactoid purpura, pericarditis, and exactication of systemic lupus erythematosus. Dislaig fontenals in infants and benign intracranial hypersension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the fitted in the internal of the conditions of the con

drig was discontinued. Ilod: Hemolytic anemia, thrombocytopenia, neutropenia, and cosinophilia have been reported with tetracyclines.

When given over protonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abhormalities of thyroid function are nown to occur.

DOSAGE AND ADMINISTRATION

DOBAGE AND ADMINISTRATION
THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF
THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the
first day of treatment cadministered 100 mg every 12 burns)
followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single, dose og as
50 mg every 12 bours, In the management of more severe

aance dose may be administered as, a single, dose og, as 150 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended. For pediatric patients above eight years of ages. The recommended of the productive patients weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by L.mg/lb of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 2 mg/lb of body weight may be used. For pediatric patients wer 100 pounds, the usual adult dose should be used. Uncomplicated, gonococcal infections in adults (except anometal infections in men): 100 mg, by mouth, twice-a-day for 7.days. As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose. The dose may be administered with food, including milk or carbonated beverage, as required.

ated beverage, as required.

acca beverage, as required.

Acute epididymo-orchits caused by N. gonorrhocae: 100 mg,
by mouth, twice-a-day for at least 10 days.

Primary and secondary syphilis: 300 mg a day in divided
deses for at least 10 days.

deses for at least 10 days.

Uncomplicated urethral, endocervical, or rectal infection in

Edults caused by Chlamydia trachomatis: 100 mg by mouth,
twice-a-day for at least 7 days.

Nangonococcal urethritis caused by C. trachomatis and U.

Acute epididymo-orchitis caused by C. trachomatis: 100 mg, by mouth, twice-a-day for at least 10 days.²
Inhalational anthrax (post-exposure):

ADULTS: 100 mg, of doxycycline, by mouth, twice a day for

60 days.

CHILDREN: weighing less than 100 lb (45 kg); 1 mg/lb (22 mg/kg) of body weight, by mouth, twice a day for 60 days. Children weighing 100 lb or more should receive the

The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage. When used in streptococcal infections, therapy should be

continued for 10 days.

Administration of adequate amounts of fluid along with capminimetation of annual endomined in the tetracycline class is resommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration (see ADVERSE RE-ACTIONS section).

My gastric irritation occurs, it is recommended that doxycycline be given with food or milk. The absorption of daxycycline is not markedly influenced by simultaneous in-

restion of food or milk.

Concomitant therapy: Antacids containing aluminum, caltum or magnesium, sodium bicarbonate, and iron-contain-ing preparations should not be given to patients taking oral Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

HOW SUPPLIED

NOW SUPPLIED

100 mg DORYX® (coated doxycycline hyclate pellsts)
Capsules have a dark yellow transparent body, with light
blue opaque cap; the capsule bearing the inscription
"DORYX" and "WC" in a circle, printed in white. Pellets are
colored yellow. Each capsule contains specially coated
pellets of doxycycline hyclate equivalent to 100 mg of
doxycycline, supplied in:

STORAGE CONDITIONS
Store at controlled room temperature below 25°C (77°F).

REFERENCES.

1. NCCLS Approved Standard:
M2-A3, Vol. 4, Performance Standards for Antimicrobial Disk Susceptibility Tests, Third Edition: available from the National Committee for Clinical Laboratory Standards, 771. Fast Lancaster Avenue, Villanova, Pa. 19085.
2. CDC Sexuality Transmitted Diseases Treatment, Guidelines 1909.

lines 1982

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